Safety Data Sheet

Me-CCNU (Semustine)

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS TOXIC, CARCINOGENIC, TERATOGENIC, AND MUTAGENIC. IT IS READILY ABSORBED BY VARIOUS BODY TISSUES THROUGH THE RESPIRATORY AND INTESTINAL TRACTS. IT MAY IRRITATE THE SKIN AND EYES. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

Introductory Note

The structural formula of Me-CCNU[A] (see B3) makes it obvious that two stereoisomers exist, namely a cis- and a trans- form. Very little has been published on cis-Me-CCNU, but it appears that in the preparation of Me-CCNU the trans- isomer is either the only or the vastly preponderant form. It may be assumed that all information on "Me-CCNU" refers to the trans- isomer.

[A]Abbreviation used in this Data Sheet. Other abbreviations used are: CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; BCNU, 1,3-bis (2-chloroethyl)-nitrosourea.

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A. Background

Me-CCNU (semustine) is a powder, stable in pure form and in solution at slightly acid pH, readily decomposed in strong acid and in alkaline solution. It is toxic in mammalian species tested (oral and parenteral toxicity in the mg/kg range) and carcinogenic, mutagenic, and probably teratogenic. Because of its high lipid solubility, which permits penetration of the "blood-brain barrier," its major use is as an anti-neoplastic, alone or in combination with other therapeutic agents, in the treatment of primary and metastatic brain tumours in addition to other malignancies, such as Lewis lung tumor and L1210 leukemia. Toxic side effects are on the hematopoietic system, the gastro-intestinal tract and particularly the kidney. Its mechanism of action consists of alkylating and carbamoylating reactions with nucleic acids, probably mainly after metabolic conversion to hydroxylated metabolites.

General reviews include: Mayo et al. (1972), Carter et al. (1972), Schabel (1976).

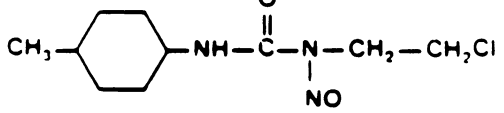
B. Chemical and Physical Data

Note: There is very little information in the literature concerning the physical and chemical properties of Me-CCNU. In what appears below such specific data are identified by an asterisk (*). For the rest, data published here are based on the much more voluminous information on CCNU which is chemically and physically similar to Me-CCNU.

1. *Chemical Abstract No.: trans: 33073-59-5; cis: 33185-87-4; unspecified: 13909-09-6

2. *Synonyms: 1-(2-chloroethyl)-3-(4-methyl-cyclohexyl)-1-nitrosourea; N-(2-chloroethyl)-N'-(trans-4-methylcyclohexyl)-N-nitrosourea; methyl-CCNU; NCI-C04955; NSC-95441; urea, N-(2-chloroethyl-N'-(4-methylcyclohexyl) N-nitroso.[A]

3. *Chemical Structure and Molecular Weight:



$C_{10}H_{18}ClN_3O_2$ 247.76

4. Density: No data.

[A]Chemical Abstracts name, used for listing in 9th Decemial Index and subsequently.

*Absorption spectroscopy: Visible and ultraviolet: Absorbance maxima at 242 (major peak), 383, 398 and 415 nm (Pavlik et al., 1983). Infrared data have been published (Johnston et al., 1971). Fluorescence (λ_{ex}=300, λ_{em}=340 nm) has been shown but is too weak for use in visualization on TLC (Pavlik et al., 1983).

Volatility: No data, may be regarded as essentially nonvolatile.

*Solubility: Very slightly soluble in water, soluble in absolute ethanol, lipids, and nonpolar organic solvents. Lipid solubility is higher than that of CCNU as indicated by a higher octanol-water partition coefficient (log P = 3.30; Hansch et al., 1972). Formulations for parenteral injections are usually in mixtures of propylene glycol and ethanol (Schaeppi et al., 1976) or in ethanol solution of a non-ionic surfactant (Davignon et al., 1973).

Description: No data but probably a white to yellowish powder.

*Boiling point: No data; melting point: 150°C (for cis- form: 112°C) (Johnston et al., 1971).

Stability: This has been recently reviewed (Bosanquet, 1985). In analogy with CCNU, Me-CCNU may be expected to be stable in dry form in unopened vials for at least two years (PDR, 1980). Storage at refrigerator temperature is recommended. In aqueous solution or suspension, maximal stability may be expected at pH 3-4 with marked decomposition at higher and lower pH values. A scheme for the decomposition of CCNU (and, by implication, of Me-CCNU) has been proposed (Colvin et al., 1976).

Chemical reactivity: The rate of decomposition of Me-CCNU is markedly higher in serum than in aqueous buffered solution; the mechanism appears to be catalysis by serum albumin of the conversion of Me-CCNU to reactive species (Weinkam et al., 1980 a,b Addition of lipoproteins to serum inhibits this catalysis. Me-CCNU like CCNU, interacts with DNA by alkylation and with peptides and proteins by carbamoylation. This has been reviewed recently (Reed, 1984). The methylcyclohexyl structure is subject to biological hydroxylation, a reaction which has been postulated to convert Me-CCNU to the ultimate reactive species (see F3).

Flash point: No data.

Autoignition temperature: No data.

Explosive limits in air: No data.

Fire, Explosion, and Reactivity Hazard Data

1. Me-CCNU is likely to be inactivated under conditions of fire. Fire-fighting personnel should wear protective clothing and face masks.

2. Flammability is likely to be low.

3. Conditions contributing to instability are acid, alkali, and elevated temperatures.

4. Hazardous decomposition products under conditions of fire are likely to include hydrochloric acid and nitrogen oxides. The formation of 2-chloroethanol, acetaldehyde, vinyl chloride, and cyclohexylamine in varying amounts has been reported for the aqueous hydrolysis of CCNU (Reed et al., 1975). The same products (with substitution of 4-methyl cyclohexylamine) are probably formed from Me-CCNU and may also be decomposition products on ignition.

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving Me-CCNU.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

Solutions of CCNU, and therefore probably also those of Me-CCNU penetrate various glove materials (Laidlaw et al., 1984). This factor should be taken into account when handling Me-CCNU.

1. Chemical inactivation: No validated method reported.

2. Decontamination: Turn off equipment that could be affected by Me-CCNU or the materials used for cleanup. Call the NIH Fire Department (dial 116) for assistance. Wipe off surfaces with ethanol, then wash with copious quantities of water.

Glassware should be rinsed (in a hood) with ethanol, followed by soap and water. Animal cages should be washed with water.

3. Disposal: No waste streams containing Me-CCNU shall be disposed of in sinks or general refuse. Surplus Me-CCNU or chemical waste streams contaminated with Me-CCNU shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing Me-CCNU shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing shall be Me-CCNU disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with Me-CCNU shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associat with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing Me-CCNU shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid Me-CCNU in unopened vials, preferably under refrigeration. Avoid exposure to light and moisture. Store working quantities of Me-CCNU and its solutions in an explosion-safe refrigerator in the work area. See B10 for further information.

E. Monitoring and Measurement Procedures including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: As for CCNU, it is important that blood samples be immediately cooled in ice, centrifuged while cold, and then extracted. Tissue samples are frozen and homogenized (Lee and Workman, 1983).

2. Analysis: Early analyses were based on colorimetry, employing the Griess or Bratton-Marshall reagent after acid liberation of nitrous acid in the presence of sulfanilamide (Loo and Dion, 1965; DeVita et al., 1967)[A] This method is capable of measuring plasma levels down to 1 µg/ml, a sensitivity which, because of the fast disappearance of intact Me-CCNU from the blood stream, is not sufficient for monitoring patients for more than 5-10 minutes after oral or intravenous administration. In addition, the method also measures active metabolites of Me-CCNU (Weinkam and Liu, 1982) unless

[A] These methods were developed for BCNU but should be applicable to Me-CCNU also.

further modified by extraction (Kari et al., 1980). Reversed phase high-pressure liquid chromatography with ultraviolet detection has been used for plasma analysis of CCNU and should also be useable for Me-CCNU (Lee and Workman, 1983). Gas chromatography methods after derivatization include trifluoroacetylation after treatment with peroxyacetic acid (Caddy and Idowu, 1982) or 2,4-dinitro-β-phenylethylamine (Caddy and Idowu, 1984), the latter with a sensitivity of 0.1 µg/ml urine or 0.08 µg/ml plasma. Sensitivity is further enhanced by subjecting these derivatives to gas chromatography-mass spectrometry (Smith et al., 1981; Smith and Cheung, 1982).

ological Effects (Animal and Human)

Absorption: Me-CCNU is quickly absorbed and produces biological effects after parenteral (intravenous, intraperitoneal) injection and by ingestion. There are no data concerning percutaneous absorption of Me-CCNU.

Distribution and pharmacokinetics: (With the exception of one study (Sponzo et al., 1973) there are no data in the literature concerning the tissue distribution of Me-CCNU; consequently, what follows is based on analogy with such studies on CCNU whose resul should be qualitatively if not quantitatively applicable.) Because of the rapid chemical and biochemical decomposition and oxidative transformation of Me-CCNU in plasma and tissues shortly after administration, distribution data based on radio-labelled material refer to hydrolytic or oxidative metabolites rather than to intact Me-CCNU. Radioactivity, after oral administration to man, was demonstrated within 10 min in plasma, with peak levels in 1-6 hours (Sponzo et al., 1973). In animals, significant quantities of radioactivity are found in all tissues, including brain and cerebrospinal fluid, within a short time after administration and are similar regardless of position of label or route of administration. Preferential distribution is to fat, liver, and brain (Oliverio et al., 1970; Litterst et al., 1974; Levin et al., 1978; Russo et al., 1984). Differences have been found in the tissue distribution of radioactivity due to labels in the methyl-cyclohexyl and the chloroethyl groups (Kramer et al., 1985). Pharmacokinetic data (for CCNU) have been published (Lee et al., 1985).

Metabolism and excretion: Me-CCNU disappears from plasma rapidly after oral or parenteral administration, and it has been assumed that its fate in vivo is similar to its decompositio in aqueous solution. Schemes for its decomposition including suggested mechanisms for the non-specific catalysis of decomposition by serum proteins (see also B11) have been

published (e.g., Weinkam et al., 1980) and these indicate the formation of chloroethyl carbonium ion as an alkylating agent, and 4-methylcyclohexyl isocyanate as a carbamoylating agent. Excretion of radioactivity due to variously (ethylene, carbonyl, methylcyclohexyl) labeled Me-CCNU is mostly in the urine; 30 and 60% of total administered radioactivity appears within 12 and 48 hours, respectively (Sponzo et al., 1973). Tissue levels of Me-CCNU are maintained longer than is the case for CCNU, and much longer than for BCNU (Kari et al., 1980). In analogy with the metabolism of CCNU one would expect excretion products to include respiratory CO_2 and urinary 4-methylcyclohexylamine and bis(4-methylcyclohexyl)urea.

In addition to these, essentially hydrolytic products of Me-CCNU metabolism, there has also been demonstrated in vitro monohydroxylation by rat liver microsomes and by purified enzyme systems. Metabolites, in decreasing amounts, are cis-4, cis-3, trans-4-methyl, trans-4-hydroxymethyl, and trans-3-hydroxyl derivatives in addition to the α-hydroxy-β-chloroethyl derivative of Me-CCNU (Hill et al., 1975; May et al., 1979; Potter et al., 1984). Many of these metabolites have been found in the urine after Me-CCNU administration to rats. Other urinary products of metabolism are thiol conjugates (thiodiacetic acid, S-carboxymethyl cysteine) derived from the alkylating moiety (Kohlhepp et al., 1981).

Toxic effects: There are no data on the acute LD50 of Me-CCNU but it may be assumed to be of the same order (40-70 mg/kg by various routes) as that of CCNU. The minimal lethal intravenous dose in dogs is 14 mg/kg (Schaeppi et al., 1976), and the LD10 (intravenous) in mice is 50 mg/kg (Kari et al., 1980). As with other alkylating agents, the onset of symptoms is prolonged and no deaths occur earlier than 4-5 days after administration of even massive doses.

Toxic effects in dogs and monkeys (Schaeppi et al., 1976) and in man (Schilsky, 1984) have been described. Me-CCNU produces hematopoietic effects (erythropenia, thrombopenia, leukopenia), bone marrow suppression, and gastroenteritis in mice (Denine et al., 1977) and other species. While there is little or no hepatotoxicity (in contrast with CCNU) the most marked toxic effect are found in the kidney which appears to be the principal target of Me-CCNU toxicity; effects include interstitial nephritis and general chronic progressive nephropathy even after a single dose (Schaeppi et al., 1976; Kramer and Boyd, 1983). It is interesting to note that Me-CCNU metabolites are preferentially accumulated in the kidney (Kramer et al., 1985). In the rabbit, topical Me-CCNU acts as a skin and eye irritant (Murphy et al., 1979).

The mechanism of toxic (and anticarcinogenic) action consists of alkylation and carbamoylation of DNA and proteins, resulting in decrease or cessation of incorporation of precursors into DNA and RNA and inhibition of protein synthesis. (Little work along these lines dealing specifically with Me-CCNU has been published but it is reasonable to assume that such action would be the same as with the well-documented effects of CCNU.)

5. Carcinogenic effects: Me-CCNU is less active in inducing lung carcinomas than CCNU or BCNU (Zeller et al., 1982) but does increase the incidence of tumors (subcutaneous fibroma, peritonea sarcoma) 1.5-2 fold over control values in rats (Weisburger, 1977

6. Mutagenic and teratogenic effects: Me-CCNU is mutagenic in the Ames test (Auletta et al., 1978; Franza et al., 1980). Teratogenicity has not been reported but in view of positive resu with CCNU it is likely to be teratogenic also.

Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.

2. Ingestion: Drink plenty of water or milk. Induce vomiting. Refer for gastric lavage.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician. Consider treatment for kidney involvement.

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